PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	09 OCT 2008
Applicant's or agent's file reference 112911.02902	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 07/82833	29 October 2007 (29.10.2007)	30 October 2006 (30.10.2006)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C07K 2/00; G01N 33/48; G06N 3/00 (2008.04)
USPC - 530/323; 703/11

Applicant THE TRUSTEES OF THE UNIVERSITY OF PRINCETON

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	1 October 2008 (01.10.2008)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 07/82833

Box No. 1 Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

   [X] the international application in the language in which it was filed.

   [ ] a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. [ ] This opinion has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established on the basis of:

   a. type of material

      [ ] a sequence listing

      [ ] table(s) related to the sequence listing

   b. format of material

      [ ] on paper

      [ ] in electronic form

   c. time of filing/furnishing

      [ ] contained in the international application as filed

      [ ] filed together with the international application in electronic form

      [ ] furnished subsequently to this Authority for the purposes of search

4. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 07/82833

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	26-29, 38	YES
	Claims	1-25, 30-37,39-42	NO
Inventive step (IS)	Claims	none	YES
	Claims	1-42	NO
Industrial applicability (IA)	Claims	1-42	YES
	Claims	none	NO

2. Citations and explanations:

Claim 26-29 and 38 lacks novelty according to PCT Article 33(3) as anticipated by the publication "Structure of Protein Phosphatase 2A Core Enzyme Bound to Tumor-Inducing Toxins" by Xing et al. (hereinafter "Xing").

As to claim 26, Xing teaches a protein phosphatase.2A (PP2A) three-dimensional structure corresponding to atomic coordinates derived from at least a portion of an atomic model of protein phosphatase 2A (PP2A) holoenzyme or protein phosphatase 2A (PP2A) holoenzyme bound to microcystin-LR (pg 342 fig 1D; three dimensional structure of PP2A bound to microcystin-LR). Furthermore, Xing teach a compound okadaic acid that can mimic the binding of microcystin-LR (pg 346 left col para 1."okadaic acid and microcystin-LR bind to the same surface pocket on the catalytic subunit of PP2A").

As to claim 27, Xing further teaches the molecule as inhibitor is okadaic acid which is an inhibitor of PP2A (pg 343 left col para 3.okadaic acid and microcystin are potent inhibitors of PP2A; pg 346 left col para 1."okadaic acid and microcystin-LR bind to the same surface pocket on the catalytic subunit of PP2A").

As to claim 28, Xing further teaches the molecule okadaic acid has a three-dimensional structure corresponding to atomic coordinates of at least a portion microcystin-LR or a combination thereof bound to protein phosphatase 2A (PP2A) holoenzyme (pg 342 fig 1 C and D; three dimenstonal structure of PP2A bound to microcystin-LR and aiso other molecule okadaic acid) ; and wherein the compound makes interactions with the catalytic (C) subunit of protein phosphatase 2A (PP2A) holoenzyme that correspond to at least a portion of the interactions observed between the catalytic (C) subunit of protein phosphatase 2A (PP2A) holoenzyme and microcystin-LR (pg 346 right col para 1; molecular details of toxin interaction with PP2A in active site of catalytic subunit Indicating that the binding sites of microcystin and okadaic acid are the same)

As to claim 29, Xing further teaches the molecule binds protein phosphatase 2A (PP2A) at a binding site for microcystin-LR on the catalytic (C) subunit of PP2A (pg 346 left col para 1."okadaic acid and microcystin-LR bind to the same surface pocket on the catalytic subunit of PP2A").

As to claim 38, Xing teaches that the molecule as okadaic acid binds to at least a portion of protein phosphatase 2A (PP2A) holoenzyme with a greater affinity than a naturally occurring substrate (pg 346 right col para 2; "Okadaic acid exhibits an IC50 of approximately 0.1 nM for PP2A").

Claims 17, 18, 39 and 40 lack an inventive step according to PCT Article 33(3) as obvious over Xing.

As to claim 17, Xing teaches an effective amount of a compound as microcystin or okadaic acid having a three-dimensional structure corresponding to atomic coordinates of at least a portion of PP2A (pg 342 fig 1D.three dimensional structure of PP2A bound to microcystin -LR; pg 353.right col Accession Numbers. "The atomic coordinates of the PP2A core enzyme bound to okadaic acid and microcystin have been deposited in the Protein Data Bank with the ID codes 2IE4 and 2IE3, respectively"). Xing does not teach a pharmaceutically acceptable excipient carrier. However, a skilled artisan would have readily appreciated that pharmaceutically acceptable excipient carriers are readily available and routine laboratory procedure to utilize. Consequently, it would have been obvious to one skilled in the art to combine an effective amount of a compound having a three dimensional structure corresponding to atomic coordinates of at least a portion of PP2A with a pharmaceutically acceptable excipient in order to utilize it for clinical purposes

As to claim 18, Xing further teaches the compound as microcystin or okadaic acid binds to PP2A holoenzyme (pg 343 left col para 3.okadaic acid and microcystin are potent inhibitors of PP2A; pg 346 left col para 1."okadaic acid and microcystin-LR bind to the same surface pocket on the catalytic subunit of PP2A").

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Supplemental Box

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Box V2.

As to claim 39, Xing further teaches the molecule as okadaic acid inhibits protein phosphatase 2A (PP2A) by binding to the active site (pg 343 left col para 3Lokadaic acid and microcystin are potent inhibitors of PP2A; pg 346 left col para 1L"okadaic acid and microcystin-LR bind to the same surface pocket on the catalytic subunit of PP2A"). Consequently, a skilled artisan would have immediately appreciated that interaction at the active site by okadaic acid would have interfered with normal enzymatic function of PP2A as a serine and threonine phosphatase.

As to claim 40, Xing does not teach a pharmaceutically acceptable excipient carrier. However, a skilled artisan would have readily appreciated that pharmaceutically acceptable excipient carriers are readily available and routine laboratory procedure to utilize and would have done so if the molecule were to be used for clinical studies.

Claims 1-13, 16, 19-25, 30-37, 41 and 42 lack an inventive step according to PCT Article 33(3) as obvious over Xing in view WO/2006/015258 A2 to Joshua-Tor (hereinafter "Joshua-Tor").

As to claim 1, Xing teaches A method for preparing a PP2A modulating compound comprising:
applying a three-dimensional molecular modeling algorithm to the atomic coordinates of at least a portion of PP2A holoenzyme (pg 342 fig 1D; Structure of the PP2A core enzyme bound to microcystin-LR (MCLR)") determining spatial coordinates of the at least a portion of PP2A holoenzyme (pg 344 Table 1.Statistic from Crystallographic Analysis; pg 353 right col Accession Numbers. "The atomic coordinates of the PP2A core enzyme bound to OA and MCLR have been deposited in the Protein Data Bank with the ID codes 2IE4 and 2IE3, respectively"). Xing does not teach electronically screening stored spatial coordinates of candidate compounds, identifying a similar compound, or synthesizing it. However, Joshua-Tor teaches electronically screening stored spatial coordinates of candidate compounds against the spatial coordinates of a protein (pg 5 ln 2-4; "The method may further comprise electronically screening the stored spatial coordinates of a set of candidate agents against the spatial coordinates of the. protein") identifying a compound that is substantially similar to the at least a portion of PP2A holoenzyme; and synthesizing the identified compound (pg 42 ln 18-20; "If computer modeling indicates a strong interaction, the molecule may then be synthesized and tested for its ability to bind to the protein and inhibit its activity"). Joshua-Tor does not teach screening, identifying, or synthesizing a compound(s) against PP2A specifically. However, a skilled artisan would readily appreciate that the method taught by Joshua-Tor could be applied to any protein for which the X-ray crystal structure was available, including PP2A. It would have been obvious to one skilled in the art to combine the three dimensional coordinates of at least a portion of the PP2A holoenzyme, as taught by Xing, with the electronic screening stored spatial coordinates of candidate compounds, identifying relevant compounds, and then synthesizing them, as taught by Joshua-Tor, because it would have provided a rationale means of identifying compounds that modulate the structure or function of PP2A.

As to claim 2, Joshua-Tor further teaches identifying a candidate compound that deviates from the atomic coordinates of the at least a portion of PP2A holoenzyme by a root mean square deviation of less than about 10 angstroms (pg 29 ln 4-6; "have a root mean square deviation ("r.m.s.d.") of less than or equal to about 1.5 Angstrom when superimposed").

As to claim 3, Joshua-Tor further teaches testing the identified compound for binding at least a portion of PP2A (pg 42 ln 18-20; "If computer modeling indicates a strong interaction, the molecule may then be synthesized and tested for its ability to bind to the protein and inhibit its activity").

As to claim 4, Joshua-Tor further teaches testing the identified compound for inhibiting PP2A activity (pg 42 ln 18-20; "if computer modeling indicates a strong interaction, the molecule may then be synthesized and tested for its ability to bind to the protein and inhibit its activity").

As to claim 5, neither Xing nor Joshua-Tor teach testing the identified compound inhibits tyrosine phosphorylation, serine phosphorylation, threonine phosphorylation or a combination thereof catalyzed by PP2A holoenzyme. However, Xing teaches protein phosphatase 2A (PP2A) belongs to the PPP family and is a major serine/threonine phosphatase involved in many essential aspects of cellular function (pg 341 left col para 2). A skilled artisan would have readily appreciated that serine and/or threonine activity as an obvious target to test with any candidate inhibitor compound and would have tested its effect on enzyme function.

As to claim 6, Joshua-Tor further teaches the step of electronically screening stored spatial coordinates further comprises identifying a compound that has a shape, a charge distribution, a size or a combination thereof substantially similar to a portion of PP2A holoenzyme (pg 42 ln 23-25; "In this screening, the quality of fit of such entities or compounds to the binding site may be judged either by shape complementarity or by estimated interaction energy").

As to claim 7, Xing further teaches that at least a portion of the PP2A holoenzyme comprises an interface between anyone of: scaffolding (A) subunit and catalytic (C) subunit (pg 344 left col para 2; "Interface between catalytic and scaffolding subunits").

As to claim 8, Xing further teaches the identified compound interrupts the interface and inhibits PP2A holoenzyme assembly (pg 350 fig 6B.A model for the formation of PP2A holoenzyme.amino acids predicted to be at the interface between the scaffolding subunit and other subunits are highlighted in red").

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As to claim 9, Joshua-Tor further teaches the identified compound binds PP2A Holoenzyme ((pg 42 ln 18-20; "if computer modelling indicates a strong interaction, the molecule may then be synthesized and tested for its ability to bind to the protein and inhibit its activity").

As to claim 10, Xing teaches a method for preparing a PP2A modulating compound comprising:
applying a three-dimensional molecular modeling algorithm to the atomic coordinates of a portion of PP2A holoenzyme corresponding to a concave surface of a regulatory subunit (pg 342 fig 1D; Structure of the PP2A core enzyme bound to microcystin-LR (MCLR)") determining spatial coordinates of the at least a portion of PP2A holoenzyme (pg 344 Table 1LStatistic from Crystallographic Analysis; pg 353 right col Accession NumbersL "The atomic coordinates of the PP2A core enzyme bound to OA and MCLR have been deposited in the Protein Data Bank with the ID codes 2IE4 and 2IE3, respectively"). Xing does not teach electrontcally screening stored spatial coordinates of candidate compounds substantially complimentary to the concave surface of the PP2A holoenzyme regulatory subunit, Identifying a compound substantially complementary to the concave surface of PP2A holoenzyme regulatory subunit, and synthesizing it. However, Joshua-Tor teaches electronically screening stored spatial coordinates of candidate compounds substantially complimentary to the concave surface of the PP2A holoenzyme regulatory subunit (pg 5 ln 2-4; "The method may further comprise electronically screening the stored spatial coordinates of a set of candidate agents against the spatial coordinates of theL protein") Identifying a compound that is substantiially complementary to the concave surface of the PP2A holoenzyme regulatory subunit ; and synthesizing the identified compound (pg 42 ln 18-20L "if computer modeling indicates a strong Interaction, the molecule may then be synthesized and tested for its ability to bind to the protein and inhibit its activity"; pg 41 ln 23-25L"In this screening, the quality of fit of such entities or compounds to the binding site may be judged either by shape complementarity or estimated Interaction energy "). Joshua-Tor does not teach screening, identifying, or synthesizing a compound(s) against PP2A specifically. However, a skilled artisan would readily appreciate that the method taught by Joshua-Tor could be applied to any protein for which the X-ray crystal structure was available, including PP2A. It would have been obvious to one skilled in the art to combine the three dimensional coordinates of at least a portion of the PP2A holoenzyme regulatory subunit, as taught by Xing, with the electronic screening stored spatial coordinates of candidate compounds, Identifying relevant compounds, and then synthesizing them, as taught by Joshua-Tor, because it would have provided a rationale means of identifying compounds that modulate the structure or function of PP2A regulatory subunit.

As to claim 11, Joshua-Tor further teaches identifying a compound that has a shape, a charge distribution, a size or a combination thereof substantially complementary to the concave surface of PP2A holoenzyme regulatory (B) subunit (pg 42 ln 23-25; "In this screening, the quality of fit of such entities or compounds to the binding site may be judged either by shape complementarity or by estimated Interaction energy").

As to claim 12, Xing further teaches the Identified compound comprises a plurality of basic motettes (pg 346 left col para 2; "an Identical set of amino acids In the catalytic subunit of PP2A mediate a simtar set of interactions with both Inhibitors. For example, the guanidium group of Arg89 donates two hydrogen bonds to different oxygen
atoms in OA and in MCLR").

As to claim 13, Xing further teaches the identified compound Inhibits entry of
substrate into an active site of PP2A catalytic (C) subunit (pg 347 fig 4A; "OA [okadaic acid] binds to the active-site pocket of the catalytic subunit").

As to claim 16, Jacob-Tor further teaches testing the Indentified compound for binding (pg 42 ln 18-20L "if computer modeling indicates a strong Interaction, the molecule may then be synthesized and tested for its ability to bind to the protein and inhibit its activity"). A skilled artisan would have readily recognized the universality of the method of Jabob-Tor and would have used and applied it to PP2A.

As to claim 19, Joshua-Tor teaches a processor; and a processor readable storage medium In communication with the processor readable storage medium comprisng the atomic coordinates of a protein of particular Interest (pg 5 ln 14-15; The application also provides a computer-readable storage medium encoded with the atomic coordinates of a. protein"). Joshua-Tor does not teach the coordinates of PP2A specifically. However, Xing teaches the coordinates for at least a portion of PP2A holoenzyme (pg 344 Table 1.Statistic from Crystallographic Analysis; pg 353 right col Accession Numbers. "The atomic coordinates of the PP2A core enzyme bound to OA and MCLR have been deposited In the Protein Data Bank with the ID codes 2IE4 and 2IE3, respectively".) A skilled artisan would readily appreciate that the system taught by Joshua-Tor could be applied to any protein for which the X-ray crystal structure was available, including PP2A and would have further appreciated this would have enabled electronic screening to Identify compounds with similar or complimentary structures. Consequently, it would have been obvious to one skilled In the art to combine the processor readable storage medium, as taught by Joshua-Tor, with the specific coordinates of PP2A, as taught by Xing, because it would have enabled electronic screening of candidate compound modulators with similar or complementary structures.

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As to claim 20, Joshua-Tor further teaches the processor readable storage medium further comprises one or more programming instructions for: applying a three-dimensional modeling algorithm to the atomic coordinates of PP2A holoenzyme (pg 4 ln 30-31; " may comprise applying a 3- dimensional molecular modeling algorithm to the atomic coordinates of a. protein to determine the spatial coordinates of the binding pocket of the .protein") determining spatial coordinates of at least a portion of the PP2A holoenzyme; electronically screening spatial coordinates of candidate compounds with the spatial coordinates of the at least a portion of thePP2A holoenzyme; and identifying a candidate compound whose spatial coordinates are substantially similar to the spatial coordinates of the at least a portion of the PP2A holoenzyme (pg 5 ln 2-5; " The method may further comprise electronically screening the stored spatial coordinates of a set of candidate agents against the spatial coordinates of the. protein . to identify agents that can bind to the . protein") or identifying a candidate compound whose spatial coordinates are substantially complementary to the spatial coordinates of the at least a portion of the PP2A holoenzyme (pg 5 ln 2-5.against the spatial coordinates of the . protein binding pocket to identify agents that can bind to the .protein.; pg 41 ln 23-25."In this screening, the quality of fit of such entities or compounds to the binding site may be judged either by shape complementarity ").

As to claim 21, Joshua-Tor further teaches the one or more programming instructions for identifying a candidate compound whose spatial coordinates are substantially similar to the spatial coordinates of the at least a portion of the PP2A holoenzyme comprise one or more programming instructions for identifying a compound that deviates from the spatial coordinates of the at least a portion of the PP2A holoenzyme by a user defined threshold (pg 29 in 4-6; "have a root mean square deviation ("r.m.s.d.") of less than or equal to about 1.5 Angstrom when superimposed").

As to claim 22, Joshua-Tor further teaches the one or more programming instructions for identifying a compound whose spatial coordinates are substantially similar to the at least a portion of the PP2A holoenzyme comprise one or more programming instructions for identifying a compound having one or more of: a size within a user defined threshold; a charge within a user defined threshold; or a shape with a user defined threshold (pg 42 ln 23-25; "In this screening, the quality of fit of such entities or compounds to the binding site may be judged either by shape complementarity or by estimated interaction energy").

As to claim 23, Joshua-Tor further teaches the one or more programming instructions for electronically screening spatial coordinates of a candidate compound comprises one or more programming instructions for simulating binding of the candidate compound to the PP2A holoenzyme (pg 42 ln 18-20; "if computer modeling indicates a strong interaction, the molecule may then be synthesized and tested for its ability to bind to the protein and inhibit its activity"; pg 45 ln 18-19. Specific computer software is available in the art to evaluate compound deformation energy and electrostatic interaction).

As to claim 24, Joshua-Tor further teaches an output device in communication with the processor (pg 27 ln 8-10; "A variety of data storage structures are available to a skilled artisan for creating a computer readable medium having recorded thereon the atomic structure coordinates of the application or portions thereof and/or X-ray diffraction data".

As to claim 25, Joshua-Tor further teaches the processor readable storage medium further comprises one or more programming instructions for: applying a three-dimensional modeling algorithm to the atomic coordinates of PP2A holoenzyme (pg 4 ln 30-31; " may comprise applying a 3- dimensional molecular modeling algorithm to the atomic coordinates of a. protein to determine the spatial coordinates of the binding pocket of the .protein"); determining spatial coordinates of at least a portion of the PP2A holoenzyme; generating a visual signal and relaying the-visual signal to the output device (pg 27 ln 5-7; Cartesian coordinates, that can be read by a scanning device and converted into a three-dimensional structure with an Optical Character Recognition (OCR)); and electronically designing a compound that is substantially similar to the at least a portion of the PP2A holoenzyme (pg 5 ln 2-5; " The method may further comprise electronically screening the stored spatial coordinates of a set of candidate agents against the spatial coordinates of the. protein . to identify agents that can bind to the . protein"); or electronically designing a compound that is substantially complementary to the at least a portion of the PP2A holoenzyme (pg 41 ln 23-25."In this screening, the quality of fit of such entities or compounds to the binding site may be judged either by shape complementarity ").

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As to claim 30, Xing does not teach the molecule has a shape, a charge, a size or combinations thereof substantially corresponding to a portion of protein phosphatase 2A (PP2A) holoenzyme. However, Joshua-Tor teaches that electronic screening of dimensional shape and charge of candidate compounds ((pg 5 ln 2-5.against the spatial coordinates of the . protein binding pocket to identify agents that can bind to the .protein.; pg 41 ln 23-25."In this screening, the quality of fit of such entities or compounds to the binding site may be judged either by shape complementarity or estimated interaction energy "). It would have been obvious to one skilled in the art to combine the spatial coordinates of at least a portion of the holoenzyme, as taught by Xing, with the electronically screening stored spatial coordinates of candidate compounds, as taught by Joshua-Tor, because it would have enabled identification of molecules that would bind to the same site as microcystin-PP2A complex.

As to claim 31, Xing further teaches the molecule binds to a catalytic (C) subunit of protein phosphatase 2A (PP2A) (pg 346 left col para 1."okadaic acid and microcystin-LR bind to the same surface pocket on the catalytic subunit of PP2A").

As to claim 32, Joshua-Tor further teaches the molecule has a shape, a charge, a size or combinaltons thereof substantially complementary to a portion of protein phosphatase 2A (PP2A) holoenzyme (pg 41 ln 23-25."In this screening, the quality of fit of such entities or compounds to the binding site may be judged either by shape complementarity estimated interaction energy ").

As to claim 33, Xing does not teach a molecule that is substantially complementary to a portion of a scaffolding(A) subunit of protein phosphatase 2A (PP2A) holoenzyme. However, Joshua-Tor teaches identifying a candidate compound whose spatial coordinates are substantially complementary to the spatial coordinates of the at least a portion of the PP2A holoenzyme (pg 5 ln 2-5.against the spatial coordinates of the . protein binding pocket to identify agents that can bind to the .protein.; pg 41 ln 23-25."In this screening, the quality of fit of such entities or compounds to the binding site may be judged either by shape complementarity or estimated interaction energy "). A skilled artisan would have immediately appreciated that the method of Joshua-Tor could be utilized to electronically screen for molecules complementary to a portion of the scaffolding subunit of PP2A. Consequently, it would have been obvious to one skilled in the art to combine the teaching of Xing in regards to having available coordinates for the scaffolding subunit of PP2A with the teaching of Joshua-Tor as to comparing the electronically comparing the coordinates of candidate compounds against the coordinates of the scaffolding subunit in order to identify complimentary molecules.

As to claim 34, Xing further teaches of the unusual flexibility of the scaffolding subunit (pg 348 left col para 2; conformational flexibility of scaffolding subunit) but does not teach a molecule that binds to scaffolding (A) subunit of PP2A holoenzyme and inhibits flexibility of the scaffolding (A) subunit. Xing further teaches the observed conformational flexibility in the scaffolding subunit of the PP2A core enzyme may have significant functional implications (pg 348 right col para 2). Consequently, a skilled artisan would have readily appreciated that identification of a complimentary molecule which binds to the scaffolding subunit, as taught in claim 33, would have an impact on its flexibility and thus its ability to interact with the catalytic subunit. Consequently, it would have been obvious to one skilled in the art to utilize a screen that selects for the inability of the scaffold subunit to interact with the catalytic subunit to identify ligands that inhibit scaffolding subunit flexibility.

As to claim 35, Xing does not teach a molecule that is substantially complementary to a portion of a regulatory subunit of protein phosphatase 2A (PP2A) holoenzyme. However, Joshua-Tor teaches identifying a candidate compound whose spatial coordinates are substantially complementary to the spatial coordinates of the at least a portion of the PP2A holoenzyme (pg 5 ln 2-5.against the spatial coordinates of the . protein binding pocket to identify agents that can bind to the .protein.; pg 41 ln 23-25."In this screening, the quality of fit of such entities or compounds to the binding site may be judged either by shape complementarity or estimated interaction energy "). A skilled artisan would have immediately appreciated that the method of Joshua-Tor could be utilized to electronically screen for molecules complementary to a portion of the regulatory subunit of PP2A. Consequently, it would have been obvious to one skilled in the art to combine the teaching of Xing in regards to having available coordinates for the scaffolding subunit of PP2A with the teaching of Joshua-Tor as to comparing the electronically comparing the coordinates of candidate compounds against the coordinates of the regulatory subunit in order to identify complimentary molecules.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 07/82833

Supplemental Box

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As to claim 36, Xing further teaches a molecule as SV40 little antigen that inhibits access of substrate to the active site of protein phosphatase 2A (PP2A) holoenzyme (pg 343 left col para 1; " the small and middle tumor antigens of polyoma virus compete with the regulatory B subunits for binding to the PP2A core enzyme").

As to claim 37, Xing further teaches the molecule inhibits formation of an active protein phosphatase2A holoenzyme (pg 343 left col para 1. the small and middle tumor antigens of polyoma virus compete with the regulatory B subunits for binding to the PP2A core enzyme; pg 342 fig 1A.by competing with the regulatory subunit, polyoma tumor antigen prevents formation of holoenzyme).

As to claim 41, Joshua-Tor further teaches the molecule deviates from the atomic coordinates of the at least a portion of PP2Aholoenzyme by a root mean square deviation of less than about 10 angstroms (pg 29 ln 4-6; "have a root mean square deviation ("r.m.s.d.") of less than or equal to about 1.5 Angstrom when superimposed").

As to claim 42, Joshua-Tor further teaches the molecule deviates from the atomic coordinates of the at least a portion ofPP2A holoenzyme by a root mean square deviation of less than about 2 angstroms (pg 29 ln 4-6; "have a root mean square deviation ("r.m.s.d.") of less than or equal to about 1.5 Angstrom when superimposed").

Claims 14-15 lack an inventive step according to PCT Article 33(3) as obvious over Xing, in view of Joshua-Tor, in further view of the publication " Use of Penetrating Peptides Interacting with PP1/PP2A Proteins As a General Approach for a Drug Phosphatase Technology" by Guergnon et al. (herelnafter "Guergnon")

As to claim 14, Xing does not teach identifying one or more PP2A substrate proteins; isolating at least a portion of the one or more PP2A substrate proteins where PP2A holoenzyme is likely to bind the one or more PP2A substrate proteins; determining spatial coordinates of the at least a portion of the one or more PP2A substrate proteins; and identifying a compound that is substantially similar to the at least a portion of the one or more PP2A substrate proteins. However, Guergnon teaches identifying one or more PP2A substrate proteins, isolating at least a portion of the one or more PP2A substrate proteins where PP2A holoenzyme is likely to bind the one or more substrate proteins (pg 1118 fig 2B; sequence homology of the PP2A binding sequence of SV40 virus small t antigen and bovine CK2 alpha). Furthermore, Jacob-Tor teaches Joshua-Tor teaches electronically screening stored spatial coordinates of candidate compounds against the spatial coordinates of a protein whose spatial coordinates have been determined (pg 5 ln 2-4; "The method may further comprise electronically screening the stored spatial coordinates of a set of candidate agents against the spatial coordinates of the. protein") A skilled artisan would have readily appreciated that the spatial coordinates of the at least a portion of the one or more PP2A substrate proteins could be obtained and compared with the spatial coordinates of candidate compounds. Consequently, it would have been obvious to combine the PP2A substrate proteins, as taught by Guergnon, with the method of determining the spatial coordinates of a protein and searching the coordinates of candidate compounds to identify those with similar spatial coordinates, as taught by Jacob-Tor, because it would have enabled a means to identify potential blockers of PP2A activity against certain substrates.

As to claim 15, Guergnon further teaches identifying more than one PP2A substrate protein, performing an alignment of the more than one PP2A substrate proteins, and isolating at least a portion of the more than one PP2A substrate proteins that share sequence similarity (pg 1118 fig 2B; sequence homology of the PP2A binding sequence of SV40 virus small t antigen and bovine CK2 alpha).

Claims 1-42 have industrial applicability as defined by PCT Article 33(4), because the subject matter can be used or made by industry